PATENT ABSTRACTS OF JAPAN

(11)Publication number : **08-099869**
(43)Date of publication of application : **16.04.1996**

(51)Int.Cl. **A61K 9/48**
A61K 47/04
A61K 47/22

(21)Application number : **07-219756**
(22)Date of filing : **04.08.1995**

(71)Applicant : **SHIONOGI & CO LTD**
(72)Inventor : **SAKUMA SATOSHI**
SUZUKI YUSUKE
FUJII TOSHIO
OGURA TOSHIHIRO
TAKAGISHI YASUSHI

(30)Priority
Priority number : 06204322 Priority date : **05.08.1994** Priority country : JP

(54) SOFT GELATIN CAPSULE PREVENTED FROM DETERIORATING AND ITS PRODUCTION

(57)Abstract:
PURPOSE: To obtain a hard gelatin capsule, containing a specific amount of a free radical scavenger, capable of preventing the solubility from deteriorating and insolubilizing with time, having stable medicine releasability and useful for a sustained release pharmaceutical preparation, etc.
CONSTITUTION: This hard gelatin capsule contains a free radical scavenger such as one or more selected from the group consisting of a pharmaceutically permissible salt of sulfurous acid, a pharmaceutically permissible salt of hydrogen sulfite and tocopherol, ascorbic acid, polyphosphoric acid, pyrophosphoric acid and a pharmaceutically permissible salt thereof in an amount of 0.01-5wt.% based on the total amount of the filling.

LEGAL STATUS

[Date of request for examination] 29.06.2001
[Date of sending the examiner's decision of rejection]
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]
[Date of final disposal for application]
[Patent number]
[Date of registration]
[Number of appeal against examiner's decision of rejection]
[Date of requesting appeal against examiner's decision of rejection]
[Date of extinction of right]

* NOTICES *

CLAIMS

[Claim(s)]

[Claim 1] A hard gelatine capsule agent by which denaturation characterized by containing a free radical trapping agent 0.01 to 5% of the weight to the packing whole quantity was prevented.

[Claim 2] A hard gelatine capsule agent by which denaturation according to claim 1 it is [denaturation] 0.01 − 1 % of the weight was prevented for a content of a free radical trapping agent to the packing whole quantity.

[Claim 3] A hard gelatine capsule agent by which denaturation according to claim 1 or 2 whose free radical trapping agent is at least one sort chosen as a salt which can be permitted on medicine manufacture of a sulfurous acid, a salt which can be permitted on medicine manufacture of a hydrogen sulfite, and a list from a group which consists of a salt which can be permitted on a tocopherol, an ascorbic acid, polyphosphoric acid, pyrophosphoric acids, and these medicine manufacture was prevented.

[Claim 4] A hard gelatine capsule agent by which denaturation according to claim 3 whose free radical trapping agent is a sodium sulfite was prevented.

[Claim 5] A hard gelatine capsule agent by which denaturation according to claim 3 whose free radical trapping agent is a sodium hydrogensulfite was prevented.

[Claim 6] A hard gelatine capsule agent by which denaturation according to claim 3 whose free radical trapping agent is a sodium pyrophosphate or a potassium pyrophosphate was prevented.

[Claim 7] A manufacture method of a hard gelatine capsule agent that denaturation characterized by making a free radical trapping agent contain 0.01 to 5% of the weight to the packing whole quantity in a manufacture method of a hard gelatine capsule agent was prevented.

[Claim 8] A manufacture method of a hard gelatine capsule agent that denaturation according to claim 7 it is [denaturation] 0.01 − 1 % of the weight was prevented for a content of a free radical trapping agent to the packing whole quantity.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] A soluble fall with time and insolubilization are prevented and this invention relates to the hard gelatine capsule agent which has the stable drug release nature and by which denaturation was prevented, and its manufacture method.
[0002]
[Description of the Prior Art] Into the hard gelatine capsule, a hard gelatine capsule agent is what was filled up with packing, such as a drug, and is used for various kinds of purpose, such as improvement in the handling nature of a drug. In layout of the pharmaceutical preparation which contains an unstable drug in an acid, a sustained release drug, etc., since a difference is produced in a bioavailability among the persons prescribed a medicine for the patient when it considers as a tablet, generally considering as a hard gelatine capsule agent for the purpose of the evasion is performed.
[0003] For example, in order to make small the difference of the absorption coefficient in intestines by difference of the alimentary canal internal transmigration speed of a drug, basin system coating of the granulatio of a drug is carried out with an enteric macromolecule or a water-insoluble nature macromolecule, and the method of filling up a hard gelatine capsule is often used. Moreover, in order to improve the wettability over the water of a poorly soluble drug, also when adding amphiphilic compounds, such as Tween (trade name), Span (trade name), and a polyethylene glycol (PEG), the method of making it into a hard gelatine capsule agent for evasion, such as deterioration of appearance, is used.
[0004] however, the case where a hard gelatine capsule is filled up with the amphiphilic compound which has granulatio and the polyoxyethylene chain of the drug which carried out basin system coating in the above-mentioned method -- warming -- a hard gelatine capsule may deteriorate at the time of conservation, and drug release nature may fall remarkably As this cause, the polyoxyethylene chain in compounds and amphiphilic compounds, such as PEG used as a plasticizer in the case of basin system coating and citric-acid triethyl, etc. pyrolyzes, and gelatin can consider bridge formation and carrying out a polymerization between intramolecular or a molecule by peroxidation products, such as an aldehyde which this generates.
[0005] Using the organic solvent which does not use a plasticizer in the case of coating as the above-mentioned cure is mentioned. However, this method is not desirable from being in the orientation for there to be a problem of a residual solvent and for use of an organic solvent to be regulated from viewpoints, such as environmental pollution, in recent years. Although using plasticizers which do not generate a peroxide, such as a triacetin and glycerol monostearate, is also considered, there is a defect of dispersing odors, such as an acetic-acid smell to which the bad plasticizer itself carries out acidolysis, and acid resistance and drug release nature deteriorate with time, and the plasticity of a film is not desirable too.
[0006] Moreover, the method of adding protein, such as casein, soybean protein, skim milk, and a collagen, in an encapsulation object is learned as other methods (JP,51-15094,A). However, this method does not control generation of a peroxide, since it needs to make [many] an addition for acquiring a desired effect, a capsule enlarges it and it becomes difficult to take it. Moreover, if reducing sugars, such as the lactose and powdered sugar in

which protein itself tends to carry out thermal denaturation, and white soft sugar, live together in packing, it is not the method that there is also a defect, such as causing the remarkable appearance change by the Maillard reaction, and it should be satisfied.
[0007]
[Problem(s) to be Solved by the Invention] This invention aims at offering the hard gelatine capsule agent which controls the soluble fall and the insolubilization of a hard gelatine capsule by aging of gelatin, and has the stable drug release nature and by which denaturation was prevented in view of the above-mentioned present condition.
[0008]
[Means for Solving the Problem] Paying attention to a peroxidation reaction being a free radical reaction, wholeheartedly, by carrying out minute amount addition of the compound with high activity which captures a free radical at an encapsulation object, this invention persons find out that a soluble fall and insolubilization of a hard gelatine capsule can be controlled, and came to complete this invention as a result of examination.
[0009] A summary of this invention is in a place which is made to contain a free radical trapping agent 0.01 to 5% of the weight to the packing whole quantity, and constitutes a hard gelatine capsule agent by which denaturation was prevented. In this specification, what has a free radical capture operation (free radical scavenging AKUTI Beatty; henceforth "RSA") as a "free radical trapping agent" is said. Moreover, the number of mols of a free radical which can be captured per one mol of free radical trapping agents is called RSA value. A hard gelatine capsule agent by which the denaturation of this invention was prevented comes to fill up other packing, such as the above-mentioned free radical trapping agent and a drug, and an additive, in a hard gelatine capsule.
[0010] As the above-mentioned free radical trapping agent, especially if it has a free radical capture operation, it will not be limited. A salt which can be permitted especially on an organic compound whose RSA value is 0.01 or more, inorganic compounds, and these medicine manufacture is desirable. For example, a salt which can be permitted on medicine manufacture of a sulfurous acid, a salt which can be permitted on medicine manufacture of a hydrogen sulfite, A cysteine, a glutathione, a tocopherol, an ascorbic acid, a thiamine nitrate, A riboflavin, beta carotene, acetaminophen, chlorpheniramine maleate, Chlorpromazine, pindolol, SESAMI Norian, a gossypol, an soybean saponin, a ROZUMARIN acid, geraniin, quercetine, glycyrrhizic acid, polyphosphoric acid, a pyrophosphoric acid, a metaphosphoric acid, ferric chloride, etc. can be mentioned. A salt which can be permitted among these on a tocopherol, an ascorbic acid, polyphosphoric acid, pyrophosphoric acids, and these medicine manufacture in a salt which can be permitted on medicine manufacture of a sulfurous acid, a salt which can be permitted on medicine manufacture of a hydrogen sulfite, and a list is desirable, and a sodium sulfite, a sodium hydrogensulfite, a tocopherol, a pyrophosphoric acid, a sodium pyrophosphate, a potassium pyrophosphate, etc. are still more desirable.
[0011] A content of the above-mentioned free radical trapping agent is 0.01 − 5 % of the weight to the packing whole quantity which set the above-mentioned free radical trapping agent and other packing. Since insolubilization depressor effect does not become not much large but a configuration of pharmaceutical preparation becomes large too much at reverse even if gelatine capsule insolubilization depressor effect is inadequate in it being less than 0.01 % of the weight and it exceeds 5 % of the weight, it is limited to the above-mentioned range. It is 0.01 − 1 % of the weight preferably.
[0012] Especially if it is except what contains an aldehyde as a component as packing besides the above, it will not be limited, but a drug, an additive, etc. which are generally contained in a capsule may be used suitably. Gestalten of the above-mentioned free radical trapping agent and other packing may be any, such as powder, granulatio, a half-solid, and a solution, and the above-mentioned granulatio may be coated with a basin system or an organic solvent system.

[0013] In this invention, according to combination of a drug used as packing, or an additive, the above-mentioned free radical trapping agent is chosen suitably, and if required, it can be used combining two or more sorts.

[0014] As the above-mentioned hard gelatine capsule, especially if usually used for pharmaceutical preparation, it will not be limited, for example, a No. 3 gelatine capsule etc. is used suitably.
[0015] What is necessary is to be able to perform manufacture of a hard gelatine capsule agent by which the denaturation of this invention was prevented with a conventional method, for example, to carry out simple mixing of the above-mentioned free radical trapping agent, and just to fill up pharmaceutical preparation presentation powder or pharmaceutical preparation presentation granulatio with it at this hard gelatine capsule. Depending on the case, the endocyst of this free radical trapping agent may be carried out into the above-mentioned granulatio or a coating layer.
[0016] Insolubilization of a gelatine capsule is a phenomenon produced when peroxidation products, such as an aldehyde generated from PEG used in the case of basin system coating, a polyethylene chain in an amphiphilic compound, etc., react with an amino group of gelatin and form a thin film. this invention -- setting -- warming -- a free radical generated by peroxidation of an encapsulation object in the conservation middle class with time is captured by free radical trapping agent, and a peroxidation reaction is controlled. For this reason, even if generation of an aldehyde etc. is controlled and it uses PEG etc. for packing, neither thin film formation of a gelatine capsule nor insolubilization accompanying this is produced.
[0017]
[Example] Although an example is hung up over below and this invention is explained to it in more detail, the range of this invention is not limited by these.
[0018] 2ml of sample solutions which made dissolution or homogeneity distribute a sample to the measurement 0.1M acetic-acid buffer solution (pH5.5) or the methanol of a RSA value, 1ml of 0.6mMDPPH(s) and methanol solutions, a methanol, or 2ml (pH5.5) of 0.1M acetic-acid buffer solutions were put into the stoppered test tube, 530nm absorbance change of the supernatant lightly obtained by carrying out centrifugal separation after a shaking at the room temperature was measured, and the RSA value was calculated.
[0019] The basket which was mixed to example 1 weighing bottle the 5 sections, put into it the free radical trapping agent which shows PEG6000 in the 95 sections and a table 1, and put in the empty No. 3 gelatine capsule on it was placed, and it saved for one week at 60 degrees C in the glass bottle with which they sealed it as a capsule and this mixture maintained the non-contact condition. This capsule was put in into the auxiliary tube for JP12 disintegration tests, and it put into the glassware which filled the 30ml (37 degrees C) of the JP12 2nd **** calmly the whole auxiliary tube, it was left for 5 - 6 minutes, and solubility was observed. The result is shown in a table 1.
[0020]
[A table 1]

フリーラジカル捕捉剤	溶解性
無添加	薄膜形成、不溶化
アスコルビン酸	速やかに溶解
リボフラビン	速やかに溶解
d-α-トコフェロール	速やかに溶解
硝酸チアミン	速やかに溶解
亜硫酸ナトリウム	速やかに溶解

[0021] According to the example 1, the capsule independent [PEG6000] which has not added the free radical trapping agent formed and insolubilized the thin film, but the soluble fall of a capsule was able to be completely inhibited by adding an ascorbic acid, a riboflavin, a tocopherol, a thiamine nitrate, or a sodium sulfite, respectively.
[0022] The constituent which added the various compounds shown in a table 2 into the KOTIDDO granulatio (henceforth "Mixture A") which mixed 30.0mg [of example 2 crystalline

cellulose], 10.0mg [of pyridoxine hydrochlorides], 54.0mg [of lactoses], and corn-starch 5.0mg, talc 31.5mg, Aerosil 0.3mg, 1.2mg [of magnesium stearates], and citric-acid triethyl 7.7mg, HPC-L0.5mg, and HPMC-AS38.3mg was prepared. The No. 3 gelatine capsule was filled up with this, and the elution test after conservation was performed for five days at 60 degrees C into the sealed glass bottle. It carried out with the method paddle method of a station (paddle rotational frequency 100 rotation), using the 900ml of the JP12 2nd liquid as an eluate. The result is shown in drawing 1 and drawing 2 .

[0023]

[A table 2]

化合物	配合（mg）								
	製剤A	製剤B	製剤C	製剤D	製剤E	製剤F	製剤G	製剤H	製剤I
混合物A	178.5	178.5	178.5	178.5	178.5	178.5	178.5	178.5	178.5
リン酸二水素ナトリウム	-	0.7	-	-	-	-	-	-	-
エテンザミド	-	-	0.7	-	-	-	-	-	-
アスピリン	-	-	-	0.7	-	-	-	-	-
アセトアミノフェン	-	-	-	-	0.7	-	-	-	-
システイン	-	-	-	-	-	0.7	-	-	-
ピロリン酸ナトリウム	-	-	-	-	-	-	0.7	-	-
亜硫酸ナトリウム	-	-	-	-	-	-	-	0.5	-
亜硫酸水素ナトリウム	-	-	-	-	-	-	-	-	0.5
合計	178.5	179.2	179.2	179.2	179.2	179.2	179.2	179.0	179.0

[0024] the pharmaceutical preparation B, C, and D which added the sodium dihydrogenphosphate, ethenzamide, or aspirin which does not have the free radical capture operation in the pharmaceutical preparation A list of Mixture A, respectively according to the example 2 -- warming -- insolubilization of a capsule was produced after conservation and drug release nature fell remarkably. the pharmaceutical preparation E, F, G, H, and I which, on the other hand, added the big acetaminophen, the cysteine, the sodium pyrophosphate, sodium sulfite, or sodium hydrogensulfite of a RSA value, respectively -- warming -- insolubilization of a capsule was not produced after conservation and the fall of drug release nature was not accepted.

[0025] The free radical trapping agent shown in example 3 table 3 was mixed in the five sections, PEG4000 was mixed with 95 section mortar, and the gelatin No. 3 capsule was filled up. Packing was removed after one-week conservation at 60 degrees C in the sealed glass bottle, and the solubility of a capsule was investigated like the example 1. The result is shown in a table 3.

[0026]

[A table 3]

フリーラジカル捕捉剤	溶解性
無添加	薄膜形成、不溶化
d-α-トコフェロール	速やかに溶解
ポリリン酸	速やかに溶解
メタリン酸	速やかに溶解
グルタチオン	速やかに溶解

[0027] the case where according to the example 3 the capsule formed and insolubilized the thin film when a free radical trapping agent was not added, but it adds -- warming -- the

soluble fall of a capsule was not accepted after conservation.
[0028] The example 4 ethenzamide 10 section and tocopherol, cysteine, or sodium-sulfite 5 section was dissolved in the Tween80 (trade name) 50 section and the Span20 (trade name) 35 section. The gelatine capsule was filled up with it and the elution test was performed like the example 2 after one-week conservation at 60 degrees C into the sealed glass bottle. The result is shown in drawing 3 .
[0029] According to the example 4, when free radical trapping agents, such as a tocopherol, were not added, the capsule was insolubilized, the remarkable fall of drug release nature was accepted, but when it added, insolubilization of a capsule was not produced and the fall of drug release nature was not accepted, either.
[0030]
[Effect of the Invention] By this invention, a soluble fall with time and insolubilization are prevented, and the hard gelatine capsule agent which has the stable drug release nature and by which denaturation was prevented can be offered.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

TECHNICAL FIELD

[A technical field to which invention belongs] A soluble fall with time and insolubilization are prevented and this invention relates to a hard gelatine capsule agent which has stable drug release nature and by which denaturation was prevented, and its manufacture method.

[Translation done.]

* NOTICES *

PRIOR ART

[Description of the Prior Art] Into the hard gelatine capsule, a hard gelatine capsule agent is what was filled up with packing, such as a drug, and is used for various kinds of purpose, such as improvement in the handling nature of a drug. In layout of the pharmaceutical preparation which contains an unstable drug in an acid, a sustained release drug, etc., since a difference is produced in a bioavailability among the persons prescribed a medicine for the patient when it considers as a tablet, generally considering as a hard gelatine capsule agent for the purpose of the evasion is performed.

[0003] For example, in order to make small the difference of the absorption coefficient in intestines by difference of the alimentary canal internal transmigration speed of a drug, basin system coating of the granulatio of a drug is carried out with an enteric macromolecule or a water-insoluble nature macromolecule, and the method of filling up a hard gelatine capsule is often used. Moreover, in order to improve the wettability over the water of a poorly soluble drug, also when adding amphiphilic compounds, such as Tween (trade name), Span (trade name), and a polyethylene glycol (PEG), the method of making it into a hard gelatine capsule agent for evasion, such as deterioration of appearance, is used.

[0004] however, the case where a hard gelatine capsule is filled up with the amphiphilic compound which has granulatio and the polyoxyethylene chain of the drug which carried out basin system coating in the above-mentioned method -- warming -- a hard gelatine capsule may deteriorate at the time of conservation, and drug release nature may fall remarkably As this cause, the polyoxyethylene chain in compounds and amphiphilic compounds, such as PEG used as a plasticizer in the case of basin system coating and citric-acid triethyl, etc. pyrolyzes, and gelatin can consider bridge formation and carrying out a polymerization between intramolecular or a molecule by peroxidation products, such as an aldehyde which this generates.

[0005] Using the organic solvent which does not use a plasticizer in the case of coating as the above-mentioned cure is mentioned. However, this method is not desirable from being in the orientation for there to be a problem of a residual solvent and for use of an organic solvent to be regulated from viewpoints, such as environmental pollution, in recent years. Although using plasticizers which do not generate a peroxide, such as a triacetin and glycerol monostearate, is also considered, there is a defect of dispersing odors, such as an acetic-acid smell to which the bad plasticizer itself carries out acidolysis, and acid resistance and drug release nature deteriorate with time, and the plasticity of a film is not desirable too.

[0006] Moreover, the method of adding protein, such as casein, soybean protein, skim milk, and a collagen, in an encapsulation object is learned as other methods (JP,51-15094,A). However, this method does not control generation of a peroxide, since it needs to make [many] an addition for acquiring a desired effect, a capsule enlarges it and it becomes difficult to take it. Moreover, if reducing sugars, such as the lactose and powdered sugar in which protein itself tends to carry out thermal denaturation, and white soft sugar, live together in packing, it is not the method that there is also a defect, such as causing the remarkable appearance change by the Maillard reaction, and it should be satisfied.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

EFFECT OF THE INVENTION

[Effect of the Invention] By this invention, a soluble fall with time and insolubilization are prevented, and the hard gelatine capsule agent which has the stable drug release nature and by which denaturation was prevented can be offered.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] This invention aims at offering the hard gelatine capsule agent which controls the soluble fall and the insolubilization of a hard gelatine capsule by aging of gelatin, and has the stable drug release nature and by which denaturation was prevented in view of the above-mentioned present condition.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

MEANS

[Means for Solving the Problem] Paying attention to a peroxidation reaction being a free radical reaction, wholeheartedly, by carrying out minute amount addition of the compound with high activity which captures a free radical at an encapsulation object, this invention persons find out that a soluble fall.and insolubilization of a hard gelatine capsule can be controlled, and came to complete this invention as a result of examination.
[0009] A summary of this invention is in a place which is made to contain a free radical trapping agent 0.01 to 5% of the weight to the packing whole quantity, and constitutes a hard gelatine capsule agent by which denaturation was prevented. In this specification, what has a free radical capture operation (free radical scavenging AKUTI Beatty; henceforth "RSA") as a "free radical trapping agent" is said. Moreover, the number of mols of a free radical which can be captured per one mol of free radical trapping agents is called RSA value. A hard gelatine capsule agent by which the denaturation of this invention was prevented comes to fill up other packing, such as the above-mentioned free radical trapping agent and a drug, and an additive, in a hard gelatine capsule.
[0010] As the above-mentioned free radical trapping agent, especially if it has a free radical capture operation, it will not be limited. A salt which can be permitted especially on an organic compound whose RSA value is 0.01 or more, inorganic compounds, and these medicine manufacture is desirable. For example, a salt which can be permitted on medicine manufacture of a sulfurous acid, a salt which can be permitted on medicine manufacture of a hydrogen sulfite, A cysteine, a glutathione, a tocopherol, an ascorbic acid, a thiamine nitrate, A riboflavin, beta carotene, acetaminophen, chlorpheniramine maleate, Chlorpromazine, pindolol, SESAMI Norian, a gossypol, an soybean saponin, a ROZUMARIN acid, geraniin, quercetine, glycyrrhizic acid, polyphosphoric acid, a pyrophosphoric acid, a metaphosphoric acid, ferric chloride, etc. can be mentioned. A salt which can be permitted among these on a tocopherol, an ascorbic acid, polyphosphoric acid, pyrophosphoric acids, and these medicine manufacture in a salt which can be permitted on medicine manufacture of a sulfurous acid, a salt which can be permitted on medicine manufacture of a hydrogen sulfite, and a list is desirable, and a sodium sulfite, a sodium hydrogensulfite, a tocopherol, a pyrophosphoric acid, a sodium pyrophosphate, a potassium pyrophosphate, etc. are still more desirable.
[0011] A content of the above-mentioned free radical trapping agent is 0.01 - 5 % of the weight to the packing whole quantity which set the above-mentioned free radical trapping agent and other packing. Since insolubilization depressor effect does not become not much large but a configuration of pharmaceutical preparation becomes large too much at reverse even if gelatine capsule insolubilization depressor effect is inadequate in it being less than 0.01 % of the weight and it exceeds 5 % of the weight, it is limited to the above-mentioned range. It is 0.01 - 1 % of the weight preferably.
[0012] Especially if it is except what contains an aldehyde as a component as packing besides the above, it will not be limited, but a drug, an additive, etc. which are generally contained in a capsule may be used suitably. Gestalten of the above-mentioned free radical trapping agent and other packing may be any, such as powder, granulatio, a half-solid, and a solution, and the above-mentioned granulatio may be coated with a basin system or an organic solvent system.

[0013] In this invention, according to combination of a drug used as packing, or an additive,

the above-mentioned free radical trapping agent is chosen suitably, and if required, it can be used combining two or more sorts.
[0014] As the above-mentioned hard gelatine capsule, especially if usually used for pharmaceutical preparation, it will not be limited, for example, a No. 3 gelatine capsule etc. is used suitably.
[0015] What is necessary is to be able to perform manufacture of a hard gelatine capsule agent by which the denaturation of this invention was prevented with a conventional method, for example, to carry out simple mixing of the above-mentioned free radical trapping agent, and just to fill up pharmaceutical preparation presentation powder or pharmaceutical preparation presentation granulatio with it at this hard gelatine capsule. Depending on the case, the endocyst of this free radical trapping agent may be carried out into the above-mentioned granulatio or a coating layer.
[0016] Insolubilization of a gelatine capsule is a phenomenon produced when peroxidation products, such as an aldehyde generated from PEG used in the case of basin system coating, a polyethylene chain in an amphiphilic compound, etc., react with an amino group of gelatin and form a thin film. this invention -- setting -- warming -- a free radical generated by peroxidation of an encapsulation object in the conservation middle class with time is captured by free radical trapping agent, and a peroxidation reaction is controlled. For this reason, even if generation of an aldehyde etc. is controlled and it uses PEG etc. for packing, neither thin film formation of a gelatine capsule nor insolubilization accompanying this is produced.

[Translation done.]

* NOTICES *

EXAMPLE

[Example] Although an example is hung up over below and this invention is explained to it in more detail, the range of this invention is not limited by these.
[0018] 2ml of sample solutions which made dissolution or homogeneity distribute a sample to the measurement 0.1M acetic-acid buffer solution (pH5.5) or the methanol of a RSA value, 1ml of 0.6mMDPPH(s) and methanol solutions, a methanol, or 2ml (pH5.5) of 0.1M acetic-acid buffer solutions were put into the stoppered test tube, 530nm absorbance change of the supernatant lightly obtained by carrying out centrifugal separation after a shaking at the room temperature was measured, and the RSA value was calculated.
[0019] The basket which was mixed to example 1 weighing bottle the 5 sections, put into it the free radical trapping agent which shows PEG6000 in the 95 sections and a table 1, and put in the empty No. 3 gelatine capsule on it was placed, and it saved for one week at 60 degrees C in the glass bottle with which they sealed it as a capsule and this mixture maintained the non-contact condition. This capsule was put in into the auxiliary tube for JP12 disintegration tests, and it put into the glassware which filled the 30ml (37 degrees C) of the JP12 2nd **** calmly the whole auxiliary tube, it was left for 5 - 6 minutes, and solubility was observed. The result is shown in a table 1.
[0020]
[A table 1]

フリーラジカル捕獲剤	溶解性
無添加	薄膜形成、不溶化
アスコルビン酸	速やかに溶解
リボフラビン	速やかに溶解
d-α-トコフェロール	速やかに溶解
硝酸チアミン	速やかに溶解
亜硫酸ナトリウム	速やかに溶解

[0021] According to the example 1, the capsule independent [PEG6000] which has not added the free radical trapping agent formed and insolubilized the thin film, but the soluble fall of a capsule was able to be completely inhibited by adding an ascorbic acid, a riboflavin, a tocopherol, a thiamine nitrate, or a sodium sulfite, respectively.
[0022] The constituent which added the various compounds shown in a table 2 into the KOTIDDO granulatio (henceforth "Mixture A") which mixed 30.0mg [of example 2 crystalline cellulose], 10.0mg [of pyridoxine hydrochlorides], 54.0mg [of lactoses], and corn-starch 5.0mg, talc 31.5mg, Aerosil 0.3mg, 1.2mg [of magnesium stearates], and citric-acid triethyl 7.7mg, HPC-L0.5mg, and HPMC-AS38.3mg was prepared. The No. 3 gelatine capsule was filled up with this, and the elution test after conservation was performed for five days at 60 degrees C into the sealed glass bottle. It carried out with the method paddle method of a station (paddle rotational frequency 100 rotation), using the 900ml of the JP12 2nd liquid as an eluate. The result is shown in drawing 1 and drawing 2 .

[0023]
[A table 2]

化合物	配合（mg）								
	製剤A	製剤B	製剤C	製剤D	製剤E	製剤F	製剤G	製剤H	製剤I
混合物A	178.5	178.5	178.5	178.5	178.5	178.5	178.5	178.5	178.5
リン酸二水素ナトリウム	−	0.7	−	−	−	−	−	−	−
エテンザミド	−	−	0.7	−	−	−	−	−	−
アスピリン	−	−	−	0.7	−	−	−	−	−
アセトアミノフェン	−	−	−	−	0.7	−	−	−	−
システイン	−	−	−	−	−	0.7	−	−	−
ピロリン酸ナトリウム	−	−	−	−	−	−	0.7	−	−
亜硫酸ナトリウム	−	−	−	−	−	−	−	0.5	−
亜硫酸水素ナトリウム	−	−	−	−	−	−	−	−	0.5
合計	178.5	179.2	179.2	179.2	179.2	179.2	179.2	179.0	179.0

[0024] the pharmaceutical preparation B, C, and D which added the sodium dihydrogenphosphate, ethenzamide, or aspirin which does not have the free radical capture operation in the pharmaceutical preparation A list of Mixture A, respectively according to the example 2 -- warming -- insolubilization of a capsule was produced after conservation and drug release nature fell remarkably. the pharmaceutical preparation E, F, G, H, and I which, on the other hand, added the big acetaminophen, the cysteine, the sodium pyrophosphate, sodium sulfite, or sodium hydrogensulfite of a RSA value, respectively -- warming -- insolubilization of a capsule was not produced after conservation and the fall of drug release nature was not accepted.
[0025] The free radical trapping agent shown in example 3 table 3 was mixed in the five sections, PEG4000 was mixed with 95 section mortar, and the gelatin No. 3 capsule was filled up. Packing was removed after one-week conservation at 60 degrees C in the sealed glass bottle, and the solubility of a capsule was investigated like the example 1. The result is shown in a table 3.
[0026]
[A table 3]

フリーラジカル捕捉剤	溶解性
無添加	薄膜形成、不溶化
d−α−トコフェロール	速やかに溶解
ポリリン酸	速やかに溶解
メタリン酸	速やかに溶解
グルタチオン	速やかに溶解

[0027] the case where according to the example 3 the capsule formed and insolubilized the thin film when a free radical trapping agent was not added, but it adds -- warming -- the soluble fall of a capsule was not accepted after conservation.
[0028] The example 4 ethenzamide 10 section and tocopherol, cysteine, or sodium-sulfite 5 section was dissolved in the Tween80 (trade name) 50 section and the Span20 (trade name) 35 section. The gelatine capsule was filled up with it and the elution test was performed like the example 2 after one-week conservation at 60 degrees C into the sealed glass bottle. The result is shown in drawing 3 .
[0029] According to the example 4, when free radical trapping agents, such as a tocopherol,

were not added, the capsule was insolubilized, the remarkable fall of drug release nature was accepted, but when it added, insolubilization of a capsule was not produced and the fall of drug release nature was not accepted, either.

[Translation done.]

* NOTICES *

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] The drug release curve of the hard gelatine capsule agent in an example 2.
[Drawing 2] The drug release curve of the hard gelatine capsule agent in an example 2.
[Drawing 3] The drug release curve of the hard gelatine capsule agent in an example 4.

[Translation done.]

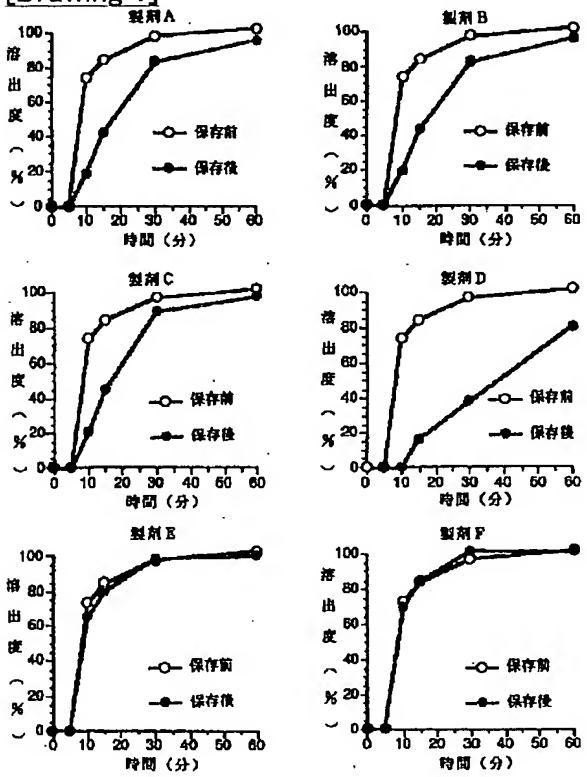
* NOTICES *

Japan Patent Office is not responsible for any damages caused by the use of this translation.

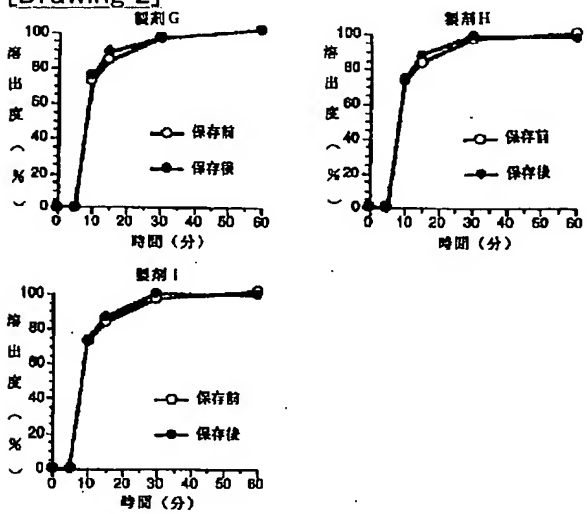
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DRAWINGS

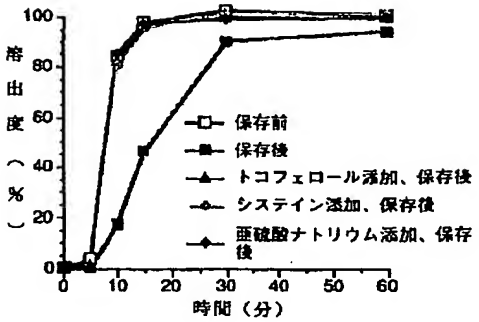
[Drawing 1]



[Drawing 2]



[Drawing 3]



[Translation done.]

(19)日本国特許庁（ＪＰ）　(12) **公開特許公報（Ａ）**　(11)特許出願公開番号

特開平8－99869

(43)公開日　平成８年(1996)４月16日

(51)Int.Cl.[6]		識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ａ６１Ｋ	9/48	Ｂ			
	47/04	Ｊ			
	47/22	Ｊ			

審査請求　未請求　請求項の数８　ＦＤ　（全 ６ 頁）

(21)出願番号　特願平7－219756

(22)出願日　平成７年(1995)８月４日

(31)優先権主張番号　特願平6－204322

(32)優先日　平６(1994)８月５日

(33)優先権主張国　日本（ＪＰ）

(71)出願人　000001926
塩野義製薬株式会社
大阪府大阪市中央区道修町３丁目１番８号

(72)発明者　佐久間　聡
大津市におの浜二丁目二番１－106

(72)発明者　鈴木　裕介
大阪府和泉市府中町５丁目15－15

(72)発明者　藤井　歳郎
兵庫県宝塚市武庫山１丁目１－１

(72)発明者　小倉　敏弘
大阪府吹田市青山台２丁目７番　Ａ４－107

(74)代理人　弁理士　安富　康男　（外１名）

最終頁に続く

(54)【発明の名称】　変性の防止された硬質ゼラチンカプセル剤及びその製造方法

(57)【要約】

【課題】　ゼラチンの経時変化による硬質ゼラチンカプセルの溶解性の低下及び不溶化を防止し、安定した薬物放出性を有する変性の防止された硬質ゼラチンカプセル剤を提供する。

【解決手段】　フリーラジカル捕獲剤を充填物全量に対して０．０１～５重量％含有する変性の防止された硬質ゼラチンカプセル剤。

1

【特許請求の範囲】

【請求項１】　フリーラジカル捕獲剤を充填物全量に対して０．０１～５重量％含有することを特徴とする変性の防止された硬質ゼラチンカプセル剤。

【請求項２】　フリーラジカル捕獲剤の含有量が、充填物全量に対して０．０１～１重量％である請求項１記載の変性の防止された硬質ゼラチンカプセル剤。

【請求項３】　フリーラジカル捕獲剤が、亜硫酸の製薬上許容しうる塩、亜硫酸水素の製薬上許容しうる塩、並びに、トコフェロール、アスコルビン酸、ポリリン酸、ピロリン酸及びこれらの製薬上許容しうる塩からなる群より選択された少なくとも１種である請求項１又は２記載の変性の防止された硬質ゼラチンカプセル剤。

【請求項４】　フリーラジカル捕獲剤が、亜硫酸ナトリウムである請求項３記載の変性の防止された硬質ゼラチンカプセル剤。

【請求項５】　フリーラジカル捕獲剤が、亜硫酸水素ナトリウムである請求項３記載の変性の防止された硬質ゼラチンカプセル剤。

【請求項６】　フリーラジカル捕獲剤が、ピロリン酸ナトリウム又はピロリン酸カリウムである請求項３記載の変性の防止された硬質ゼラチンカプセル剤。

【請求項７】　硬質ゼラチンカプセル剤の製造方法において、フリーラジカル捕獲剤を充填物全量に対して０．０１～５重量％含有させることを特徴とする変性の防止された硬質ゼラチンカプセル剤の製造方法。

【請求項８】　フリーラジカル捕獲剤の含有量が、充填物全量に対して０．０１～１重量％である請求項７記載の変性の防止された硬質ゼラチンカプセル剤の製造方法。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、経時的な溶解性の低下、不溶化が防止され、安定した薬物放出性を有する変性の防止された硬質ゼラチンカプセル剤及びその製造方法に関する。

【０００２】

【従来の技術】硬質ゼラチンカプセル剤は、硬質ゼラチンカプセル中に薬物等の充填物を充填したもので、薬物の取扱い性の向上等各種の目的で使用されている。酸に不安定な薬物を含有する製剤や徐放性製剤等の設計において、錠剤とした場合には、被投与者間でバイオアベイラビリティに差を生じるため、その回避を目的として硬質ゼラチンカプセル剤とすることが一般的に行われている。

【０００３】例えば、薬物の消化管内移動速度の相違による腸内吸収率の差を小さくするため、腸溶性高分子や水不溶性高分子で薬物の顆粒を水系コーティングし、硬質ゼラチンカプセルに充填する方法がしばしば用いられる。また、難溶性薬物の水に対するぬれ性を改善するために、Ｔｗｅｅｎ（商品名）、Ｓｐａｎ（商品名）、ポリエチレングリコール（ＰＥＧ）等の両親媒性化合物を添加する場合にも、外観の劣化等の回避のために硬質ゼラチンカプセル剤とする方法が用いられる。

2

【０００４】しかし、上記方法において、水系コーティングした薬物の顆粒やポリオキシエチレン鎖を有する両親媒性化合物を硬質ゼラチンカプセルに充填した場合、加温保存時に硬質ゼラチンカプセルが変質し、薬物放出性が著しく低下することがある。この原因としては、水系コーティングの際に可塑剤として使用されるＰＥＧ、クエン酸トリエチル等の化合物や両親媒性化合物中のポリオキシエチレン鎖等が熱分解し、これにより生成するアルデヒド等の過酸化生成物により、ゼラチンが分子内又は分子間で架橋、重合することが考えられる。

【０００５】上記の対策として、例えば、コーティングの際に、可塑剤を使用しない有機溶媒を用いることが挙げられる。しかし、この方法は、残留溶媒の問題があり、また、環境汚染等の観点から有機溶媒の使用が近年規制される傾向にあることから、望ましいものではない。過酸化物を生成しないトリアセチン、グリセリンモノステアレート等の可塑剤を用いることも考えられるが、フィルムの形成性が悪い、可塑剤自体が酸分解し経時的に耐酸性や薬物放出性が劣化する、酢酸臭等の臭気を飛散する等の欠点があり、やはり好ましいものではない。

【０００６】また、他の方法として、カプセル充填物にカゼイン、大豆タンパク質、スキムミルク、コラーゲン等のタンパク質を添加する方法が知られている（特開昭５１－１５０９４号公報）。しかし、この方法は、過酸化物の生成を抑制するものではなく、所望の効果を得るには添加量を多くする必要があるため、カプセル剤が大型化して服用が困難となる。また、タンパク質自体が熱変性しやすい、乳糖、粉糖、白糖等の還元糖が充填物中に共存していると、メイラード反応による著しい外観変化をきたす、等の欠点もあり、満足すべき方法ではない。

【０００７】

【発明が解決しようとする課題】本発明は、上記現状に鑑み、ゼラチンの経時変化による硬質ゼラチンカプセルの溶解性の低下及び不溶化を抑制し、安定した薬物放出性を有する変性の防止された硬質ゼラチンカプセル剤を提供することを目的とするものである。

【０００８】

【課題を解決するための手段】本発明者らは、過酸化反応がフリーラジカル反応であることに着目し、鋭意検討の結果、フリーラジカルを捕獲する活性の高い化合物をカプセル充填物に微量添加することにより、硬質ゼラチンカプセルの溶解性の低下や不溶化を抑制することができることを見いだし、本発明を完成するに至った。

【０００９】本発明の要旨は、変性の防止された硬質ゼ

ラチンカプセル剤を、フリーラジカル捕獲剤を充填物全量に対して０．０１～５重量％含有させて構成するところにある。本明細書において、「フリーラジカル捕獲剤」とは、フリーラジカル捕獲作用（フリーラジカル・スカベンジング・アクティビィティ；以下「ＲＳＡ」ともいう）を有するものをいう。また、フリーラジカル捕獲剤１モルあたり捕獲することができるフリーラジカルのモル数を、ＲＳＡ値という。本発明の変性の防止された硬質ゼラチンカプセル剤は、硬質ゼラチンカプセル内に上記フリーラジカル捕獲剤及び薬物、添加剤等の他の充填物を充填してなる。

【００１０】上記フリーラジカル捕獲剤としては、フリーラジカル捕獲作用を有しているものであれば特に限定されず、なかでもＲＳＡ値が０．０１以上である有機化合物、無機化合物及びこれらの製薬上許容しうる塩が好ましく、例えば、亜硫酸の製薬上許容しうる塩、亜硫酸水素の製薬上許容しうる塩、システイン、グルタチオン、トコフェロール、アスコルビン酸、硝酸チアミン、リボフラビン、β－カロチン、アセトアミノフェン、マレイン酸クロルフェニラミン、クロルプロマジン、ピンドロール、セサミノール、ゴシポール、大豆サポニン、ロズマリン酸、ゲラニイン、ケルセチン、グリチルリチン酸、ポリリン酸、ピロリン酸、メタリン酸、塩化第２鉄等を挙げることができる。これらのうち、亜硫酸の製薬上許容しうる塩、亜硫酸水素の製薬上許容しうる塩、並びに、トコフェロール、アスコルビン酸、ポリリン酸、ピロリン酸及びこれらの製薬上許容しうる塩等が好ましく、亜硫酸ナトリウム、亜硫酸水素ナトリウム、トコフェロール、ピロリン酸、ピロリン酸ナトリウム、ピロリン酸カリウム等がさらに好ましい。

【００１１】上記フリーラジカル捕獲剤の含有量は、上記フリーラジカル捕獲剤及び他の充填物を合わせた充填物全量に対して０．０１～５重量％である。０．０１重量％未満であるとゼラチンカプセル不溶化抑制効果が不充分であり、５重量％を超えても不溶化抑制効果はあまり大きくならず、逆に製剤の形状が大きくなりすぎるため、上記範囲に限定される。好ましくは０．０１～１重量％である。

【００１２】上記他の充填物としては、成分としてアルデヒドを含有するもの以外であれば特に限定されず、カプセル剤中に一般に含有される薬物及び添加剤等が好適に用いられ得る。上記フリーラジカル捕獲剤及び他の充填物の形態は、粉末、顆粒、半固形、溶液等のいずれであってもよく、また、上記顆粒は水系あるいは有機溶媒系でコーティングしたものであってもよい。

【００１３】本発明においては、充填物として使用される薬物や添加剤の組み合わせに応じて、上記フリーラジカル捕獲剤を適宜選択し必要であれば２種以上を組み合わせて使用することができる。

【００１４】上記硬質ゼラチンカプセルとしては、通常製剤に用いられるものであれば特に限定されず、例えば、３号ゼラチンカプセル等が好適に用いられる。

【００１５】本発明の変性の防止された硬質ゼラチンカプセル剤の製造は、常法により行うことができ、例えば、上記フリーラジカル捕獲剤は、製剤組成粉末又は製剤組成顆粒に単純混合して該硬質ゼラチンカプセルに充填すればよい。場合によっては、上記顆粒内又はコーティング層内に該フリーラジカル捕獲剤を内包させてもよい。

【００１６】ゼラチンカプセルの不溶化は、水系コーティングの際に使用されるＰＥＧや両親媒性化合物中のポリエチレン鎖等から発生するアルデヒド等の過酸化生成物がゼラチンのアミノ基と反応し、薄膜を形成することにより生じる現象である。本発明においては、加温保存中等におけるカプセル充填物の経時的過酸化によって発生するフリーラジカルは、フリーラジカル捕獲剤によって捕獲され、過酸化反応が抑制される。このため、アルデヒド等の生成が抑制され、充填物にＰＥＧ等を使用しても、ゼラチンカプセルの薄膜形成や、これに伴う不溶化を生じない。

【００１７】

【実施例】以下に実施例を掲げて本発明をさらに詳しく説明するが、本発明の範囲がこれらにより限定されるものではない。

【００１８】ＲＳＡ値の測定

０．１Ｍ酢酸緩衝液（ｐＨ５．５）又はメタノールに試料を溶解又は均一に分散させた試料液２ｍｌ、０．６ｍＭＤＰＰＨ・メタノール溶液１ｍｌ、及び、メタノール又は０．１Ｍ酢酸緩衝液（ｐＨ５．５）２ｍｌを共栓付き試験管に入れ、室温で軽く振とう後、遠心分離し、得られた上澄み液の５３０ｎｍの吸光度変化を測定してＲＳＡ値を求めた。

【００１９】実施例１

秤量瓶にＰＥＧ６０００を９５部、表１に示すフリーラジカル捕獲剤を５部混合して入れ、その上に空の３号ゼラチンカプセルを入れたバスケットを置き、カプセルとこの混合物が非接触の状態を保つようにして密栓したガラス瓶中に６０℃で１週間保存した。このカプセルをＪＰ１２崩壊試験用の補助筒の中に入れ、ＪＰ１２第２液約３０ｍｌ（３７℃）を満たしたガラス容器に補助筒ごと静かに入れ、５～６分間放置して溶解性を観察した。その結果を表１に示す。

【００２０】

【表１】

5

フリーラジカル捕獲剤	溶解性
無添加	薄膜形成、不溶化
アスコルビン酸	速やかに溶解
リボフラビン	速やかに溶解
ｄ－α－トコフェロール	速やかに溶解
硝酸チアミン	速やかに溶解
亜硫酸ナトリウム	速やかに溶解

【００２１】実施例１によれば、フリーラジカル捕獲剤を添加していないＰＥＧ６０００単独のカプセルは薄膜を形成し、不溶化したが、アスコルビン酸、リボフラビン、トコフェロール、硝酸チアミン又は亜硫酸ナトリウムをそれぞれ添加することによりカプセルの溶解性の低

6

下を完全に抑止することができた。

【００２２】実施例２

結晶セルロース３０．０ｍｇ、塩酸ピリドキシン１０．０ｍｇ、乳糖５４．０ｍｇ、コーンスターチ５．０ｍｇ、タルク３１．５ｍｇ、アエロジル０．３ｍｇ、ステアリン酸マグネシウム１．２ｍｇ、クエン酸トリエチル７．７ｍｇ、ＨＰＣ－Ｌ０．５ｍｇ、ＨＰＭＣ－ＡＳ３８．３ｍｇを混合したコーティッド顆粒（以下「混合物Ａ」という）に表２に示す種々の化合物を添加した組成物を調製した。これを３号ゼラチンカプセルに充填し、密栓したガラス瓶中に６０℃で５日間保存後溶出試験を行った。溶出液としてＪＰ１２第２液９００ｍｌを用い、局方パドル法（パドル回転数１００回転）で行った。その結果を図１及び図２に示す。

【００２３】

【表２】

化合物	配合（ｍｇ）								
	製剤Ａ	製剤Ｂ	製剤Ｃ	製剤Ｄ	製剤Ｅ	製剤Ｆ	製剤Ｇ	製剤Ｈ	製剤Ｉ
混合物Ａ	178.5	178.5	178.5	178.5	178.5	178.5	178.5	178.5	178.5
リン酸二水素ナトリウム	－	0.7	－	－	－	－	－	－	－
エテンザミド	－	－	0.7	－	－	－	－	－	－
アスピリン	－	－	－	0.7	－	－	－	－	－
アセトアミノフェン	－	－	－	－	0.7	－	－	－	－
システイン	－	－	－	－	－	0.7	－	－	－
ピロリン酸ナトリウム	－	－	－	－	－	－	0.7	－	－
亜硫酸ナトリウム	－	－	－	－	－	－	－	0.5	－
亜硫酸水素ナトリウム	－	－	－	－	－	－	－	－	0.5
合　計	178.5	179.2	179.2	179.2	179.2	179.2	179.2	179.0	179.0

【００２４】実施例２によれば、混合物Ａのみの製剤Ａ並びにフリーラジカル捕獲作用を有していないリン酸二水素ナトリウム、エテンザミド又はアスピリンをそれぞれ添加した製剤Ｂ、Ｃ及びＤは加温保存後にはカプセルの不溶化を生じ、薬物放出性が著しく低下した。一方、ＲＳＡ値の大きなアセトアミノフェン、システイン、ピロリン酸ナトリウム、亜硫酸ナトリウム又は亜硫酸水素ナトリウムをそれぞれ添加した製剤Ｅ、Ｆ、Ｇ、Ｈ及びＩは加温保存後でもカプセルの不溶化を生じず、薬物放出性の低下は認められなかった。

【００２５】実施例３

表３に示すフリーラジカル捕獲剤を５部、ＰＥＧ４０００を９５部乳鉢で混合し、ゼラチン３号カプセルに充填した。密栓したガラス瓶中に６０℃で１週間保存後、充填物を除去し、実施例１と同様にしてカプセルの溶解性を調べた。その結果を表３に示す。

【００２６】

【表３】

フリーラジカル捕獲剤	溶解性
無添加	薄膜形成、不溶化
ｄ－α－トコフェロール	速やかに溶解
ポリリン酸	速やかに溶解
メタリン酸	速やかに溶解
グルタチオン	速やかに溶解

【００２７】実施例３によれば、フリーラジカル捕獲剤を添加しない場合はカプセルが薄膜を形成し不溶化したが、添加した場合は、加温保存後でもカプセルの溶解性の低下は認められなかった。

【００２８】実施例４

エテンザミド１０部及びトコフェロール、システイン又は亜硫酸ナトリウム５部を、Ｔｗｅｅｎ８０（商品名）５０部及びＳｐａｎ２０（商品名）３５部に溶解した。それをゼラチンカプセルに充填し、密栓したガラス瓶中に６０℃で１週間保存後、実施例２と同様にして溶出試

験を行った。その結果を図３に示す。

【００２９】実施例４によれば、トコフェロール等のフリーラジカル捕獲剤を添加しない場合は、カプセルは不溶化し、著しい薬物放出性の低下が認められたが、添加した場合はカプセルの不溶化は生じず、薬物放出性の低下も認められなかった。

【００３０】

【発明の効果】本発明により、経時的な溶解性の低下及び不溶化が防止され、安定した薬物放出性を有する変性の防止された硬質ゼラチンカプセル剤を提供することができる。

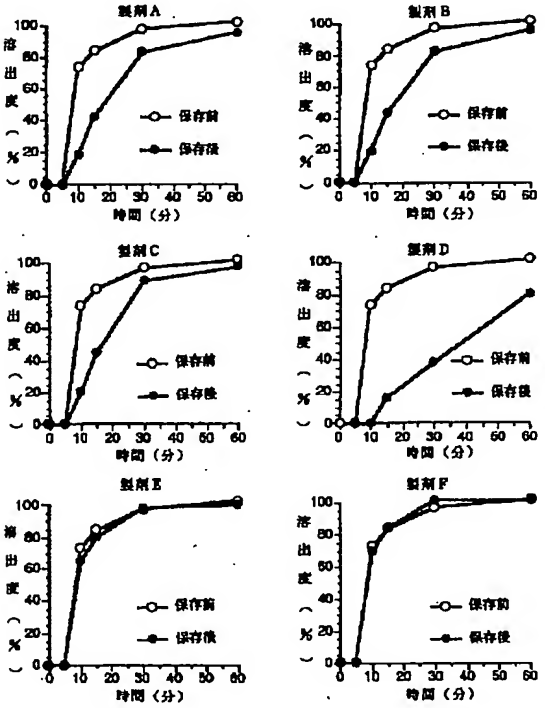
【図面の簡単な説明】

【図１】実施例２における硬質ゼラチンカプセル剤の薬物放出曲線。

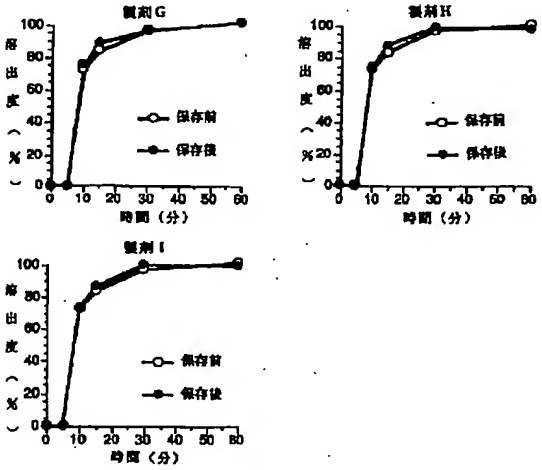
【図２】実施例２における硬質ゼラチンカプセル剤の薬物放出曲線。

【図３】実施例４における硬質ゼラチンカプセル剤の薬物放出曲線。

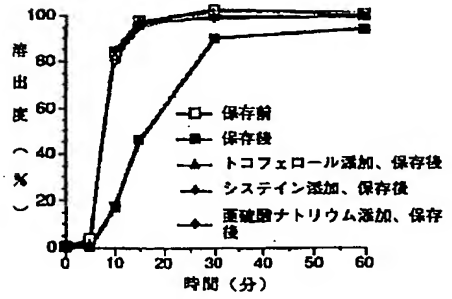
【図１】



【図２】



【図３】



フロントページの続き

(72)発明者　髙岸　靖
兵庫県芦屋市潮見町27－１